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ORIGINAL

Hirudin versus heparin for anticoagulation in continuous renal replacement therapy

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Abstract *Objective*: To compare the efficacy and safety of hirudin and heparin for anticoagulation during continuous renal replacement therapy (CRRT) in critically ill patients.
Design: Prospective, randomized controlled pilot study.
Setting: Single centre; interdisciplinary intensive care unit at a university hospital.
Patients: Seventeen patients receiving CRRT.
Interventions: Patients were randomly allocated to two groups. Heparin group (nine patients): continuous administration of 250 IU/h heparin; dose was adjusted in 125 IU/h steps with a targeted activated clotting time (ACT) of 180–210 s. Hirudin group (eight patients): continuous infusion of 10 μg/kg/h hirudin, dose was adjusted in 2 μg/kg/h steps with a targeted ecarin clotting time (ECT) of 80–100 s. Observation time was 96 h.
Measurements and main results: Measured filter run patency and haemofiltration efficacy did not significantly differ between the two groups. Three bleeding complications were observed in the hirudin group, none in the heparin group ($P < 0.01$). At the onset of bleeding, which occurred 60 or more hours after the start of therapy, only one patient was still under continuous hirudin administration but levels were either in therapeutic range or below.
Conclusions: Hirudin can be used efficiently for anticoagulation in CRRT. Late bleeding complications may have been caused by possible hirudin accumulation, but this was not evident from hirudin plasma and ECT levels. Since bleeding complications were observed only in the presence of documented coagulation disorders, not only adequate drug monitoring but also the plasmatic and cellular coagulation status of the patient should be taken into consideration for adjusting hirudin dosage.

Key words Critically ill patients · Continuous haemofiltration · Anticoagulation · Heparin · Hirudin · Efficacy · Bleeding

Introduction

The incidence of acute renal failure (ARF) varies in critically ill patients but can be as high as 25 % [1, 2, 3, 4]. A mortality rate between 50 and 90 % has been reported in patients with ARF and multiple-organ dysfunction syndrome (MODS) [3, 4, 5]. Continuous renal replacement therapy (CRRT) has become the treatment of choice for ARF in the intensive care unit (ICU) [6, 7]. The goal for anticoagulation in CRRT is to maintain patency of the extracorporeal circuit and to prolong filter life and function in the presence of minimal or absent systemic effects. The blood-system interaction tends to activate plasmatic and cellular coagulation pathways leading to possible clot formation and membrane obstruction [8]. This is the reason why antithrombogenic therapy is required during extracorporeal blood purification techniques. Heparin is the most widely used substance for anticoagulation in CRRT [9]. Heparin exerts its anticoagulant effect mainly by enhancing the effect of antithrombin III (AT III) on thrombin inactivation. However, the anticoagulant effect may sometimes be insufficient, since heparin inactivates only free thrombin and not fibrin-bound thrombin [10, 11]. On the other hand, the increase in heparin dosage may result in bleeding complications [12]. A further problem may arise by the development of heparin-induced thrombocytopenia type II (HIT II) where further anticoagulation with heparin is contraindicated. The overall incidence of HIT II has been reported to be as high as 10 % [13] with detection of heparin-induced antibodies against platelets in the patient's plasma [14]. These and other adverse effects such as hypersensitivity reactions, skin necrosis, increase in liver enzymes and HIT II-independent thrombocytopenia have led to the search for a safer and more effective anticoagulant.

Hirudin, a polypeptide made by recombinant technology, and with a molecular weight of 7,000 Da, acts independently of cofactors, and directly inhibits bound and unbound thrombin. Its elimination half-life is 1–3 h, and the elimination pathway is > 90 % unmetabolized through the kidneys. In the presence of renal failure the half-life of hirudin is considerably prolonged [15, 16]. Hirudin is removed through haemofiltration membranes at a rate dependent on the sieving coefficient of the membrane used [17, 18]. In cases of ARF, hirudin accumulation may result in possible bleeding complications. Natural hirudin was utilized as a first anticoagulant in the early times of haemodialysis, but it was soon abandoned because of life-threatening hypersensitivity reactions. Recombinant hirudin, on the contrary, has been used safely and effectively for intermittent and continuous dialysis [10, 11, 19]. There are reports, however, of severe bleeding complications under hirudin anticoagulation for renal replacement therapy [20, 21]. The importance of adequate drug dosing and coagulation monitoring is considered to be essential to avoid accumulation. Activated partial thromboplastin time (aPTT) has been considered to be an unreliable monitoring parameter during hirudin anticoagulation, because it does not correlate with hirudin levels [22]. Ecarin clotting time (ECT), a whole-blood plasma clotting-time assay based on thrombin activation through the snake venom ecarin, has shown adequate dose-response curves [22]. As coagulation disorders with bleeding complications and episodes of filter clotting are reported either with heparin or with hirudin during CRRT, the aim of the present study was to evaluate the efficacy and safety of both regimes in a randomized, controlled, comparative trial carried out in patients treated with CRRT.

Materials and methods

After ethical committee approval and written informed consent from a legal representative, 20 critically ill patients with ARF and indication for CRRT were enrolled in this prospective, controlled, single-centre, open-labelled, randomized clinical trial. Exclusion criteria were age < 18 years, pregnancy, acute head injury, acute bleeding and HIT II. Enrolled patients were randomly allocated into two groups. Three patients were excluded from the study after enrolment due to immediate surgery in one case and due to haemodynamic instability with pending surgery in two cases. Therefore, nine patients completed the study in the heparin group and eight patients in the hirudin group. All patients were sedated, mechanically ventilated and given additional therapy according to the ICU standard protocol. ARF was defined as a urine output < 500 ml/24 h in spite of adequate fluid resuscitation and an increase in creatinine (normal: < 115 μmol/l) and urea (normal: 2.3–7.6 mmol/l) of three-times the normal values.

A double-lumen venous catheter (Large-Bore catheter, 1.8 mm diameter, Arrow International, Reading Pa., USA) in the jugular, subclavian or femoral vein was used for vascular access. Continuous pump-driven veno-venous haemofiltration (CVVH) was performed with a Polyflux 11 S, 1.1 m^2 haemofilter (Gambro Dialysatoren, Hechingen, Germany) and BM 11 + BM 14 equipment (Baxter, McGaw Park, Ill., USA). Pump-driven blood flow in the extracorporeal circuit was maintained at 80–150 ml/min. Ultrafiltrate was replaced by infusion of haemofiltration solution after the filter (post-dilution mode) at a rate of 1,000–2,000 ml/h). Anticoagulants were administered into the extracorporeal system before the haemofilter.

The heparin group received heparin (Liquemin N, Roche, Grenzach-Wyhlen, Germany) with an initial dose of 250 IU/h. The extracorporeal system was rinsed with 3 l of heparinized saline (10,000 IU of heparin) during the priming procedure. The anticoagulation therapy was monitored every 4h using the activated clotting time (ACT) (HemoTEG ACT, Englewood Colo., USA). An ACT of 180–210 s was targeted and subsequent heparin dose adjustments were made using steps of 125 IU/h.

The hirudin group received 10 μg/kg/h hirudin (Refludan, Aventis Pharma, Bad Soden im Taunus, Germany) initially. The extracorporeal system was rinsed during the priming procedure with 3 l of saline containing 100 μg of hirudin. The anticoagulation therapy was monitored every 4 h with the ECT (Thrombostat 2, Behnk Elektronik, Norderstedt, Germany). An ECT of 80–100 s was targeted and subsequent hirudin dose adjustments were made

Table 1 Basic patient characteristics and indications for continuous renal replacement therapy *(CRRT)*. *APACHE III* acute physiology and chronic health evaluation III, *MODS* multiple-organ dysfunction syndrome score

Parameter	Heparin ($n = 9$)	Hirudin ($n = 8$)	P
Age (years) [median (range)]	61 (19–80)	67 (46–81)	> 0.99
Gender (male/female)	8/1	7/1	0.61
APACHE III baseline [median (range)]	66 (51–106)	66 (36–85)	0.64
MODS baseline [median (range)]	7 (4–15)	8 (5–14)	0.96
Diagnosis *(n)*			
Acute heart failure	4	2	0.62
Sepsis	4	5	0.63
Multiple injured patient	1	1	> 0.99
Indications for CRRT			
Acute renal failure	7	6	> 0.99
Other causes	2	2	> 0.99
Creatinine (μmol/l) [median (range)]	254 (113–533)	178 (59–420)	0.27
Urea (mmol/l) [median (range)]	22 (8–29)	33 (2–43)	> 0.99

using steps of 2 μg/kg/h. The observation time was 96 h. ECT and ACT, haemoglobin (Hb) and platelet count (Technicon H3, Bayer Diagnostics, Fernwald, Germany), aPTT and prothrombin time (PT) (STA, Roche Diagnostics, Mannheim, Germany) and blood gas analysis including electrolytes and lactate (ABL 500, Radiometer, Copenhagen, Denmark) were measured every 4 h. Creatinine and urea (Hitachi 744 E, Roche Diagnostics, Mannheim, Germany) were determined on a daily basis. Haemofiltration efficacy regarding blood purification was determined as the relative decrease in serum levels of creatinine and urea [11]. The number of filter changes due to clotting or other reasons was registered. Filter patency, determined as the filter run time, was registered as filter efficacy parameter.

A bleeding complication was defined as an Hb decrease of 2 g/dl or more in the presence of estimated normovolemia and clinical signs of bleeding.

Data were expressed for the whole study as median and range. Overall values were defined as values over the whole study period. Kaplan-Meier survival curves were plotted for comparison of filter patency in both groups. Inter-group statistical analysis was performed using the Mann-Whitney-U test and for dichotomous variables using the Pearson chi-square and Fisher exact test, respectively. Intra-group statistical analysis was performed with the Wilcoxon matched-pairs signed rank sum test. A P value of < 0.05 was considered to be statistically significant.

Results

Basic patient characteristics as well as indications for CRRT and renal function parameters did not differ between groups (Table 1).

Filter patency was not significantly different between either group (hirudin 22 (4–36) h vs heparin 28 (4–56) h, $P = 0.18$). In the heparin group 43 % of filters had a filter survival > 24 h, in the hirudin group 41 % ($P = 0.89$). A survival curve for filter patency is presented in Fig. 1. Although baseline plasmatic and cellular coagulation parameters did not differ between groups, a significant difference in overall aPTT values was observed in both groups (Table 2). Overall PT was slightly but not significantly lower in the hirudin group than in the heparin group (Table 2). The intra-group statistical analysis between baseline and overall values was significantly different in the heparin group for ACT ($P = 0.03$) and platelet count ($P = 0.02$) and in the hirudin group for aPTT (0.03) and ECT ($P = 0.01$) (Table 2). No bleeding episodes were observed with heparin. In three patients in the hirudin group, bleeding complications occurred (heparin vs hirudin, $P < 0.01$) despite the fact that hirudin application was stopped in patient 1 and in patient 2 for 12 h and 4 h respectively, before the onset of bleeding. All of these three patients suffered from septic shock: patient 1 due to an abscess after laryngectomy (additional diagnosis: liver cirrhosis) and patients 2 and 3 due to pneumonia. Table 3 shows hirudin dose and plasma levels, units of packed red blood cells transfused, Hb levels, coagulation parameters, acute physiology and chronic health evaluation (APACHE) III and MODS score, norepinephrine requirements and lactate levels for all three patients at the onset of bleeding.

Haemofiltration efficacy regarding blood purification did not significantly differ between the two groups. Creatinine decrease from baseline to last value was: heparin 21 % vs hirudin 28 % ($P = 0.91$); urea decrease from baseline to last value: heparin 25 % vs hirudin 71 % ($P = 0.06$). Urea decrease was higher in the hirudin group. The difference was not significant.

Outcome did not differ between the two groups. The maximum APACHE III and MODS scores were comparable during ICU stay (Table 4).

Discussion

The most important results of this study were that hirudin can be used efficiently in CRRT as far as filter patency and blood purification are concerned. However, significantly more bleeding complications were observed developing more than 60 h after commencement of study, and 4 and 12 h after hirudin application had been

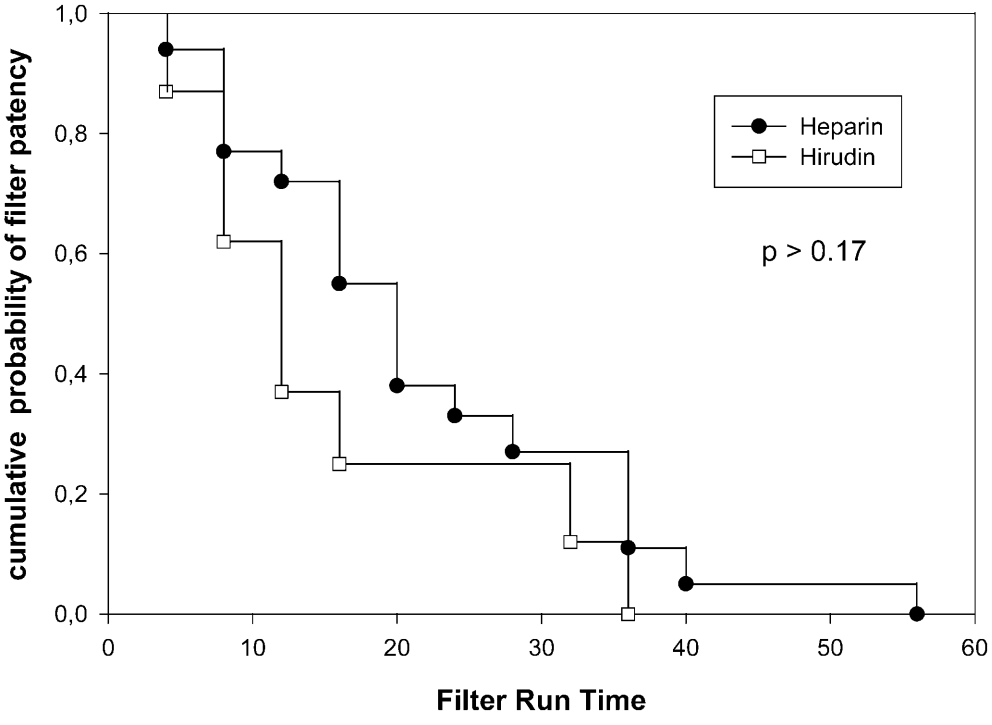

Fig. 1 Filter run time Kaplan-Meier survival curve. The difference in filter survival is not statistically different ($P > 0.17$)

discontinued. To the best of our knowledge, there are no prospective studies comparing hirudin and heparin for anticoagulation in CRRT.

Filter patency was not significantly different between groups. Hirudin provided acceptable filter survival, in the range previously reported for heparin [23]. A "brief report" from our institution on five critically ill patients receiving CRRT who were switched from heparin to hirudin because of HIT II, showed an equally favourable filter patency of 12–48 h [20]. Vanholder et al. [10] and van Wyk et al. [11] performed intermittent haemodialysis with hirudin, without clotting complications, using a bolus dose of 0.08 mg/kg and 0.15 mg/kg, respectively. van Wyk et al. found less accumulation of ^{111}In-labelled platelets in the artificial kidney during dialysis with hirudin than with heparin [24]. Taking into account the results in the literature for intermittent haemodialysis and our own in CRRT, we found that hirudin was as effective as heparin in preventing filter clotting.

Comparing basic and overall mean values for plasmatic coagulation parameters in the hirudin group, we found a possible progressive plasmatic coagulation dis-

Table 2 Basic and overall cellular and plasmatic coagulation parameters and dose *PT* prothrombin time, *aPTT* activated partial thromboplastin time, *ACT* activated clotting time, *ECT* ecarin clotting time, *AT III* antithrombin III

Parameter	Heparin ($n = 9$) Median (range)	Hirudin ($n = 8$) Median (range)	P
PT (%) baseline	69 (53–98)	63 (31–81)	0.27
PT (%) overall	75 (56–99)	59 (32–77)	0.06
aPTT (s) baseline	36 (32–84)	42 (32–45)	0.63
aPTT (s) overall	42 (32–44)	52 (43–66)*	< 0.01
ACT (s) baseline	151 (127–248)	159 (143–247)	0.44
ACT (s) overall	200 (129–221)*	194 (158–218)	0.70
ECT (s) baseline		59 (46–72)	
ECT (s) overall		83 (53–101)*	
Platelets (/nl) baseline	178 (90–294)	147 (30–204)	0.13
Platelets (/nl) overall	110 (50–292)*	140 (35–180)	0.81
AT III (%) baseline	87 (40–104)	67 (39–92)	0.39
AT III (%) overall	85 (59–109)	63 (42–100)	0.17
Fibrinogen (g/dl) baseline	490 (280–800)	420 (270–990)	0.22
Fibrinogen (g/dl) overall	420 (240–680)	410 (260–920)	0.96
Dose	250 (125–750) IU/h	299 (40–1120) µg/h	
Dose	3.3 (1.8–10) IU/kg//h	4.0 (0.5–16) µg/kg/h	

* $P < 0.05$ for intra-group statistical test baseline vs overall

Table 3 Laboratory and clinical parameters at onset of bleeding and baseline values *Hb* haemoglobin, *PT* prothrombin time, *aPTT* activated partial thromboplastin time, *ACT* activated clotting time, *ECT* ecarin clotting time, *MODS* multiple-organ dysfunction syndrome score, *APACHE III* acute physiology and chronic health evaluation III

Parameter	Patient 1	Patient 2	Patient 3
Onset of bleeding after study begin (h)	60	72	76
Hirudin dose (μg/kg/h)	0	0	5
Hirudin plasma level (μg/ml)	0.30	0.14	0.29
Blood transfusion (units)	9	3	4
Hb (g/dl)	6.0	10.7	9.3
Platelets baseline (/nl)	116	30	117
Platelets (/nl)	62	14	76
PT baseline (%)	31	68	65
PT (%)	35	58	43
aPTT baseline (s)	43	32	37
aPTT (s)	60	96	73
ACT baseline (s)	155	139	248
ACT (s)	211	234	220
ECT baseline (s)	72	63	57
ECT (s)	85	65	83
MODS	13	9	8
APACHE III	93	74	62
Norepinephrine (μg/kg/min)	0.70	0.10	0.88
Lactate (mmol/l)	17.4	3.6	3.2

Table 4 Intensive care unit *(ICU)* stay and outcome. *APACHE III* acute physiology and chronic health evaluation III, *MODS* multiple organ dysfunction syndrome score III

	Heparin ($n = 9$)	Hirudin ($n = 8$)	*P*
ICU stay (days) [median (range)]	22 (3–66)	26 (6–146)	0.96
ICU mortality *(n)*	5	6	0.71
APACHE III maximum [median (range)]	74 (50–134)	72 (36–93)	0.56
MODS maximum [median (range)]	8 (4–17)	8 (5–14)	0.93

order with a significant increase in aPTT and a rise in ACT. This led to a prolongation of filter patency independent of anticoagulation, whereas in the heparin group an inadequate increase in mean aPTT was observed (unexpectantly significantly lower than in the hirudin group). The aPTT has been discussed controversially regarding its usefulness for monitoring of CRRT anticoagulation. This is supported by Stefanidis et al., who found a significant increase in filter patency for ACT > 110 s whereas no correlation between aPTT and filter patency was found [25]. On the other hand Murray found ACT to be less sensitive than aPTT in detecting heparin anticoagulation [26].

Platelet count decreased in both groups during CRRT. It is known that platelets are consumed during CRRT because of shear forces [27]. In both groups, more than 40 % of the patients suffered from septic shock (heparin 44 %, hirudin 63 %) and in both groups one patient had suffered from multiple injuries. Both states, septic shock as well as multiple trauma, could have also accounted for the decrease in platelet count.

AT III substitution was performed in six patients in the heparin group (1,000–4,000 IU/day) when AT III levels were under 60 %. This was done because heparin effector mechanism is completely AT III-dependent, and it could be an explanation for the not-significant higher levels in the heparin group [28].

In the present study three bleeding complications were seen in the hirudin group, none in the heparin group. Postoperative bleeding complications were described by Kern et al., who described three patients with continuous hirudin infusion (0.01 mg/kg/h) and serious bleeding events [20]. Fischer et al. administered hirudin continuously (0.006–0.025 mg/kg/h), or as single dose (0.007–0.04 mg/kg), for CRRT in seven critically ill patients with suspected or confirmed HIT II without bleeding complications [19]. Both studies [19, 20] monitored hirudin therapy with a targeted aPTT of 1.5–2.0× baseline. In intermittent haemodialysis, some authors have seen bleeding complications and others have not, but a reduction in the dosage of the anticoagulant agent always led to cessation of bleeding events without reducing efficacy [10, 11, 15].

The patients with bleeding complications seen in our study, showed plasmatic and cellular coagulation disorders at the onset of bleeding which, in two cases, were already present before CRRT, and worsened as the disease progressed, compromising other coagulation pathways. The aPTT and ACT levels of the bleeding patients were far above normal values, while PT and platelets were pathologically decreased due to the underlying disease.

It is noteworthy, that in all three cases, the time of the onset of bleeding (60 h after the study began) was the same. It is known that hirudin is not metabolized, and in > 90 % is excreted by the kidneys with an unpredictable prolongation of half-life [15]. Kern et al. also observed bleeding complications several days after hirudin had been given continuously [20]. In the present study the hirudin dose at the time when bleeding started was < 5 μg/kg/h, and the ECT was 65–85 s. The determined hirudin plasma levels were < 0.30 μg/ml. These plasma levels were below therapeutic range (0.5–2.5 μg/ml) [22]. These data suggest there was no relevant accumulation of hirudin. However, hirudin was found in plasma of two patients 4 and 12 h respectively, after hirudin had been discontinued.

ECT has been described as a precise method for determining blood levels of hirudin [22, 29]. ECT registers hirudin action, but rises also when prothrombin and fi-

brinogen levels become pathologically decreased [22]. Fibrinogen levels were in the normal range or above in these patients. Unfortunately, we did not determine prothrombin levels. Assessment of hirudin therapy with aPTT has been discussed controversially, due to the lack of correlation between hirudin levels and aPTT [22, 30]. Considering the baseline values, the medical history and the clinical course of our patients, we feel that the bleeding complications were probably caused by the patients' clinical conditions of septic shock and underlying diseases, respectively. Although hirudin concentrations were low, they might have worsened the preexisting coagulopathy. Undoubtedly as important as anticoagulation monitoring is the determination of the patient's coagulation status and subsequent dose adjustment. It is possible to think of unknown interactions between preexisting coagulation disorders and hirudin. To be on the safe side it is possible to stick to bolus administration which may prove to be superior.

Efficacy, i.e. urea and creatinine decrease, did not differ significantly between the two groups. However, the decrease in urea, although not significant, tended to be more pronounced in the hirudin group. This implies that hirudin allows at least an efficient blood purification in CRRT. On the other hand, taking the lesser decrease in creatinine into account, it could point to a difference in metabolism between groups. Successful urea and creatinine excretion was also observed in intermittent haemodialysis with hirudin anticoagulation [11].

In conclusion, hirudin can be used efficiently for anticoagulation in CRRT. However, bleeding complications were observed. Therefore, the indication for anticoagulation with hirudin should be critically evaluated e.g. just for patients with any contraindication for heparin, such as HIT II. Bleeding complications developed more than 60 h after the study began, and several hours after discontinuation of hirudin administration. Bleeding was probably mainly caused by coagulopathies and not by hirudin accumulation. Therefore, not only is adequate drug monitoring required, but plasmatic and cellular coagulation status of the patient should also be monitored, to guide anticoagulation therapy with hirudin in CRRT. Severe coagulation disorders or possible risk for bleeding may definitely limit the alternative approach with continuous hirudin infusion under CRRT. For this, in critically ill patients with severe coagulation disorders, intermittent application under drug monitoring should be investigated.

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